Association of Non-Acquired Immunodeficiency Syndrome-Defining Cancers With Human Immunodeficiency Virus Infection

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Kaposi's sarcoma and non-Hodgkin's lymphoma were among the earliest recognized manifestations of the acquired immunodeficiency syndrome (AIDS) epidemic. Excluding these two tumors, the overall risk of all other cancers in human immunodeficiency virus (HIV)-infected individuals is similar to that of the general population. However, varying levels of evidence link several additional neoplasms to HIV infection. The evidence is strongest for an association with Hodgkin's disease, with lower relative and absolute risks than for non-Hodgkin's lymphoma. Anogenital intraepithelial neoplasia also appears to be HIV associated, but increases of invasive disease are still uncertain for both cervical and anal cancers. Various studies have suggested associations with testicular seminoma, multiple myeloma, oral cancer, and melanoma, but the data are inconsistent. Leiomyosarcoma and benign leiomyomas have increased in incidence in HIV-infected children but are unusual in HIV-infected adults. Conjunctival carcinoma is seen in HIV-infected individuals in sub-Saharan Africa but it is uncommon in Western countries. Most other cancers do not seem to have increased incidences in HIV infection. The etiologic mechanisms of HIV-related cancer likely differ among these diverse cancers and do not globally increase cancer risk. [Monogr Natl Cancer Inst 1998;23:23–25]

Kaposi's sarcoma and non-Hodgkin's lymphoma are relatively frequent outcomes of human immunodeficiency virus (HIV) infection. Several additional tumors appear to be associated with HIV infection, albeit with smaller relative and absolute risks. The evidence is strongest for associations of HIV with anogenital neoplasia, Hodgkin's disease, testicular seminoma, pediatric leiomyosarcoma, and conjunctival cancer. Most other cancers, however, including the carcinomas most common in the general population, do not appear to be increased in HIV infection.

Excluding Kaposi's sarcoma and non-Hodgkin's lymphoma, the overall risk of all other cancers in HIV-infected individuals is similar to that of the general population. The Viral Epidemiology Branch follows two cohorts of HIV-infected hemophilia patients. The cancer experience (through March 1991) of the 1261 HIV-infected subjects in the Multicenter Hemophilia Cohort Study has been previously reported (1). The National Cancer Institute Registry of HIV-Infected Hemophilia Patients follows an additional 1639 subjects recruited in 1991 and 1992. Through June 1996, there were a total of 7675 person-years of observation for the two cohorts combined. With the exclusion of Kaposi's sarcoma and non-Hodgkin's lymphoma, a total of 20 cases of other cancers were observed in comparison with the 13.2 expected, for a relative risk (RR) of 1.5 (95% confidence interval [CI] = 0.9–2.3). Unlike non-Hodgkin's lymphoma incidence, the incidence of other cancers did not significantly increase with the duration of HIV infection (Fig. 1).

HIV and concomitant immunosuppression has been associated with cervical carcinoma *in situ* in studies by Vermund et al. (2), Williams et al. (3), Klein et al. (4), Ho et al. (5), and others. Although cervical cancer was added to the 1993 surveillance definition for AIDS by the U.S. Centers for Disease Control and Prevention, an effect of HIV on invasive cancer is uncertain. Between 1976 and 1988, invasive cervical cancer incidence decreased approximately 40% in New York City black women, a group with a high prevalence of HIV infection (6). Furthermore, New York City AIDS cases from 1992 through 1993 had only a fourfold increase of cervical cancer relative to the general population (7), despite likely confounding by shared behavioral risk factors for HIV and human papillomavirus (HPV) infection. Similarly, there was only one case of invasive cervical cancer in 3612 woman-years of observation after AIDS in the AIDS–Cancer Match Registry (Goedert JJ: personal communication), which matches population-based cancer and AIDS registries in Puerto Rico and seven regions of the United States (8). While the impact of Pap screening is difficult to assess, a large excess risk of invasive cervical cancer seems unlikely by these data.

Anal intraepithelial neoplasia has also been associated with HIV and/or HIV-related immunosuppression in studies by Palefsky et al. (9), Kiviat et al. (10), and others. As with cervical cancer, an etiologic association of HIV with invasive anal cancer is uncertain. Incidence in single San Francisco men aged 25–54 years (a population approximately 50% homosexual) was 2.0 per 100 000 from 1973 through 1979, which was 9.9 (95% CI = 4.5–18.7) times that of the general population in the same period. Thus, even before the HIV epidemic, these men were at very high risk of invasive anal cancer. While the rate increased to 3.9 per 100 000 in 1988 through 1990, incidence in the general population increased in parallel, so the RR was virtually unchanged at 10.1 (95% CI = 5.0–18.0) times expected (11). In more recent data through 1994, the number of anal cancer cases
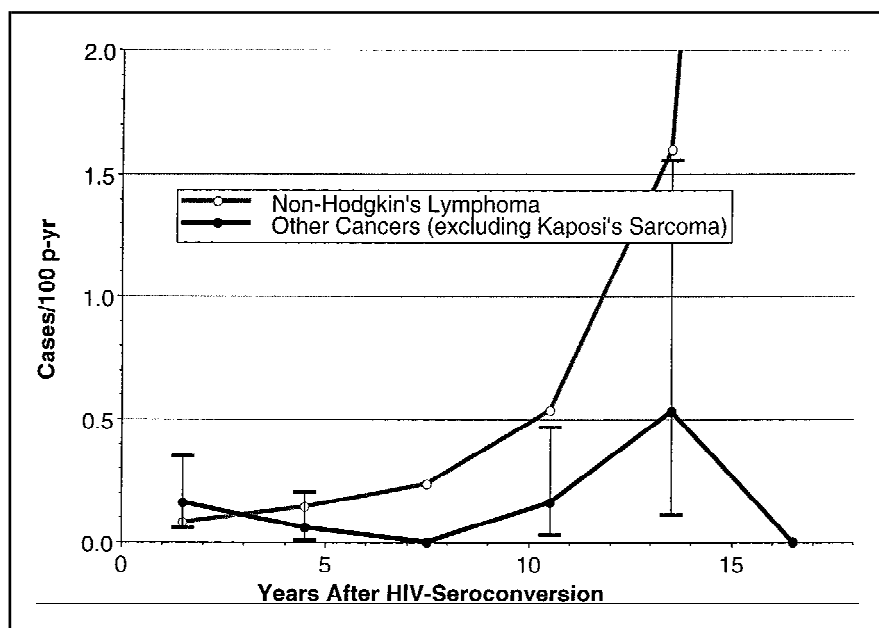
Fig. 1. Incidence of non-Hodgkin's lymphoma and of other cancers (excluding Kaposi's sarcoma) in the Multicenter Hemophilia Cohort Study by duration of HIV infection.

in San Francisco men has continued to increase. Moreover, about half of the cases since 1985 have occurred in association with AIDS, diagnosed either before or after anal cancer (Fig. 2). While these data may reflect some excess risk with advanced HIV infection, the relative excess appears to be small in comparison with the 10-fold RR predating AIDS.

Early evidence that Hodgkin's disease is increased by HIV infection came from the San Francisco City Clinic Cohort *(12)*, which has been updated in a combined analysis (total 15 565 subjects) with the New York City hepatitis B natural history and vaccine trial cohorts *(13)*. Additional evidence came from a San Francisco AIDS and cancer registry-linkage study *(14)*. These findings have been corroborated in several additional studies, including the Multicenter AIDS Cohort Study *(15)* (2683 sub-

jects, 17 780 HIV-positive person-years), the New South Wales AIDS–Cancer Match *(16)* (3616 subjects), and the National Cancer Institute hemophilia studies. The RR of Hodgkin's disease was 2.5 in the hepatitis B cohorts and ranged from 5.6 to 8.5 in the other studies; the 95% CI excluded 1.0 in all four studies (Table 1). The hepatitis cohort found the lowest risk of total non-AIDS cancers (Table 1), perhaps because cases were ascertained by matching with cancer registrations rather than by active follow-up.

The four studies are less consistent with respect to HIV-associated increases in other cancers (Table 1). An increase in testicular seminoma was previously reported in the Multicenter AIDS Cohort Study by Lyter et al. *(15)* but was not observed in the other studies. Statistically significant increases (i.e., 95% CI excluding 1.0) of multiple myeloma and oral cancer were observed in the Multicenter AIDS Cohort Study and the New South Wales AIDS–Cancer Match. Malignant melanoma was significantly increased in the Multicenter AIDS Cohort Study yet not in New South Wales where the disease is more common. These inconsistent associations warrant further investigation before being accepted or discarded.

Notably absent from this list are increases in leiomyosarcoma and squamous cell conjunctival cancer. HIV-infected children are at greatly increased risk of leiomyosarcoma and benign leiomyomas, as first noted by Chadwick et al. *(17)*. These tumors have only rarely been noted in HIV-infected adults *(18)*, despite the much larger number potentially at risk. The HIV-associated cases uniformly contain Epstein-Barr virus (EBV), leading to speculation that prior EBV infection protects HIV-infected adults from this disorder. Similarly, conjunctival squamous cell cancer is found relatively frequently in AIDS cases in sub-Saharan Africa *(19)*, yet is rare in the United States. Differences in solar ultraviolet radiation exposure or in prevalence of conjunctival HPV infection may explain the variation.
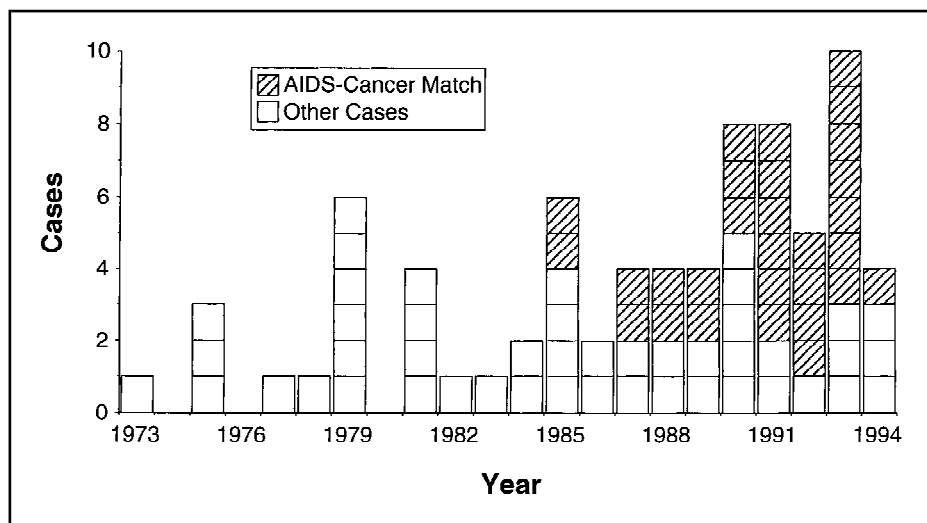
Despite their limited variety, HIV-associated tumors are likely to be diverse in their pathology and etiology. Viral cofactors, such as EBV, HPV, and human herpesvirus type 8 may play a role in some of these disorders, but not all viral-associated tumors are increased in AIDS. Notable exceptions are hepatocellular carcinoma (despite high prevalence of both hepatitis B and hepatitis C in HIV-infected hemophilia patients) and nasopharyngeal carcinoma (despite near universal prevalence of EBV). Immunodysregulation or cytokine imbalance may underlie the various tumor associations. More importantly, even advanced immunodeficiency does not appear to lead to in-

Fig. 2. Anal cancer cases and AIDS comorbidity in San Francisco County men aged 25–54 years, SEER[1] Program and AIDS–Cancer Match Registry, from 1973 through 1994. Shaded boxes = cases with AIDS at or after cancer diagnosis; unshaded boxes = difference in a given year between the total cases detected by cancer surveillance and the number detected by the AIDS–Cancer Match Registry.

Table 1. Relative risks of selected cancers in cohort- and registry-matching studies of HIV and cancer*

Cancer type or site	Cohort	No. of cases	Relative risk	95% CI
Total non-AIDS	NCI Hemophilia Cohort and Registry	20	1.5	0.9–2.3
	Multicenter AIDS Cohort Study	51	2.6	1.9–3.4
	NYC and SF Hepatitis B Studies	168	0.7	0.6–0.8
	New South Wales AIDS–Cancer Match	70	—	—
Hodgkin's disease	NCI Hemophilia Cohort and Registry	3	5.6	1.1–16
	Multicenter AIDS Cohort Study	5	6.7	2.2–16
	NYC and SF Hepatitis B Studies	18	2.5	1.5–3.9
	New South Wales AIDS–Cancer Match	10	8.5	4.1–16
Testicular seminoma	NCI Hemophilia Cohort and Registry	2	2.5	0.3–8.8
	Multicenter AIDS Cohort Study	7	3.9	1.6–8
	NYC and SF Hepatitis B Studies	9	0.5	0.2–0.9
	New South Wales AIDS–Cancer Match	4	1.2	0.3–2.9
Multiple myeloma	NCI Hemophilia Cohort and Registry	0	0	—
	Multicenter AIDS Cohort Study	3	14.2	2.9–41
	NYC and SF Hepatitis B Studies	1	0.5	0–2.8
	New South Wales AIDS–Cancer Match	4	5.8	1.2–17
Melanoma	NCI Hemophilia Cohort and Registry	3	3.7	0.8–11
	Multicenter AIDS Cohort Study	6	2.9	1.1–6.3
	NYC and SF Hepatitis B Studies	11	0.6	0.3–1.1
	New South Wales AIDS–Cancer Match	15	1.3	0.8–2.2
Oral	NCI Hemophilia Cohort and Registry	2	3.3	0.4–12
	Multicenter AIDS Cohort Study	5	3.9	1.3–9.1
	NYC and SF Hepatitis B Studies	8	0.6	0.3–1.2
	New South Wales AIDS–Cancer Match	6	4.1	1.6–9.5

*HIV = human immunodeficiency virus; NCI = National Cancer Institute; NYC = New York City; SF = San Francisco; AIDS = acquired immunodeficiency syndrome; and CI = confidence interval.

creases in most types of cancers. The spectrum of HIV-associated cancers may further develop as HIV-infected persons survive longer with highly active antiretroviral therapies. Determining the mechanisms of the specific cancers increased with HIV infection will likely advance the general understanding of cancer etiology.

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Note

[1] *Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.